

EVOLENCE®

Collagen Filler

Instructions for Use

FDA DRAFT 19 JUNE 08

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed physician, or properly licensed practitioner.

DEVICE DESCRIPTION

EVOLENCE® Collagen Filler is a porcine collagen gel implant composed of 3.5% (35 mg/ml) homogenous Type I collagen that was extracted and purified from porcine tendons and suspended in phosphate-buffered saline (PBS) and which has been cross linked with a ribose mediated (GLYMATRIX™) technology.

EVOLENCE® is supplied as single use pre-filled sterile syringe.

INDICATIONS FOR USE

EVOLENCE® Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

CONTRAINDICATIONS

EVOLENCE® Collagen Filler is contraindicated in the following:

- Patients with known hypersensitivity to any collagen products or planning to undergo desensitization injections to porcine products, as these injections can contain porcine collagen.
- Patients with a history of anaphylactic reactions or history or presence of severe recurrent allergic reactions.
- **EVOLENCE®** Collagen Filler should not be implanted in spaces other than the dermis of the face.
- **EVOLENCE®** Collagen Filler should not be implanted in patients with bleeding disorders.

WARNINGS

- Local necrosis is a rare event, which has been observed following other collagen implantation and may occur following injections to the glabella. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Patients with a history of dietary porcine allergy should be carefully examined before porcine collagen injections, since it is possible that the collagen component of the porcine material may be causing the allergy.
- Avoid injecting **EVOLENCE®** into blood vessels as collagen can initiate platelet aggregation and may cause vascular occlusion and localized infarction or embolic phenomena.

- Use of **EVOLENCE®** at specific sites in which infections or active inflammatory reaction is present, should be deferred until the underlined process has been controlled.
- Injection site reactions (e.g., swelling, redness, tenderness, or pain) to **EVOLENCE®** have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the adverse reactions section for details.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules (solid, raised skin lesions less than 1 cm in diameter) that may occur rarely should be considered and treated as a soft tissue infection.

PRECAUTIONS

The following precautions must be observed:

- **STERILE CONTENT.** The prefilled syringe is intended for single patient use. Do not resterilize. Do not use if the package is opened or damaged.
- As with all transcutaneous procedures, injection of **EVOLENCE®** carries a risk of infection. The usual precautions associated with injectable material should be followed.
- Bruising or bleeding may occur at **EVOLENCE®** injection sites. Patients using substances, which may reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs, may experience increased bruising or bleeding at injection sites as experienced with any injection.
- The safety and effectiveness of **EVOLENCE®** for the treatment of anatomic regions other than facial wrinkles and nasolabial folds has not been established in controlled clinical studies.
- The safety and efficacy of **EVOLENCE®** for lip augmentation has not been established.
- The safety of usage in breast augmentation or injection into bone, tendon, ligament or muscle has not been established in controlled clinical studies.
- **EVOLENCE®** should be used with caution in patients on immunosuppressive therapy.
- The safety of **EVOLENCE®** in pregnant or breastfeeding females, as well as in patients under 18 years of age has not been established.
- The safety of **EVOLENCE®** with concomitant dermal therapies such as epilation, UV radiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials, therefore there are no data available on the potential for site inflammatory reaction.
- Injection of **EVOLENCE®** into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Patients should minimize exposure of the treated areas to excessive sun, UV lamp exposure and extreme hot or cold weather for the first 24-48 hours following treatment.
- Based on preclinical studies the use of **EVOLENCE®** in individual patients shall be limited to 10 ml over a one year period. The safety of injecting greater amounts has not been established. In clinical trials using a split face design,

patients were injected with up to approximately 4 mL of EVOLENCE® in a single injection site over a one year time period.

- The safety of EVOLENCE® in patients susceptible to keloid formation, hyperpigmentation and hypertrophic scarring has not been established.
- Long term safety and effectiveness of EVOLENCE® beyond one year have not been investigated in clinical trials.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state, and federal requirements.
- EVOLENCE® should not be mixed with other products before implantation of the device.
- EVOLENCE® is a yellowish, homogenous, opaque gel. In the event that a syringe contains material exhibiting separation between solid and liquid, or change of color, do not use the syringe and notify OrthoNeutrogena at 1-800-386-5362.

ADVERSE EVENTS

Clinical Evaluation of EVOLENCE® Collagen Filler

A randomized, comparative trial to evaluate the safety and efficacy of EVOLENCE® was conducted at 6 clinical centers. One hundred and forty nine (149) subjects were injected with EVOLENCE® into one nasolabial fold (NLF) and the Hyaluronic Acid-based dermal filler (HA Control Product) into the contralateral NLF.

Each subject recorded treatment symptoms up to 14 days following initial injection and up to resolution of any event following the touch up facial injection in the subject's diary. Subjects were instructed to rate each common treatment response listed in the diary as Mild, Moderate, Severe or None. Each subject also was evaluated for adverse events by the study investigators at each of multiple follow-up visits.

Injection site responses (symptom related AE) reported by >5% of subjects or observed by the study investigators in either treatment group are summarized in tables 1 and 2. All observed adverse events are included; No adverse events other than those listed in Table 1 and 2 were observed by any study subject or investigator.

**Table 1: Number & (%) of Subjects with AEs at the Injection Site* by Maximum Severity
– for Adverse Events Occurring in >5% of Subjects, as
Reported in Subjects' Diaries and Physician Case Report Forms**

	EVOLENCE® (Total N = 149)				HA Control Product (Total N = 149)			
	Overall Incidence	Mild	Mod	Severe	Overall Incidence	Mild	Mod	Severe
Injection Site Conditions[†]	123 (82.6)	111 (74.5)	11 (7.4)	1 (0.7)	130 (87.2)	113 (75.8)	16 (10.7)	1 (0.7)
Pain	84 (56.4)	77 (51.7)	6 (4.0)	1 (0.7)	95 (63.8)	85 (57.0)	10 (6.7)	0
Erythema	86 (57.8)	83 (55.7)	2 (1.3)	1 (0.7)	89 (59.7)	84 (56.4)	5 (3.4)	0
Swelling	80 (53.7)	74 (49.7)	5 (3.4)	1 (0.7)	102 (68.5)	94 (63.1)	8 (5.4)	0
Bruising	54 (36.2)	52 (34.9)	2 (1.3)	0	71 (47.7)	63 (42.3)	7 (4.7)	1 (0.7)
Pruritus	23 (15.4)	23 (15.4)	0	0	25 (16.8)	25 (16.8)	0	0
Induration	20 (13.4)	17 (11.4)	3 (2.0)	0	9 (6.0)	8 (5.4)	1 (0.7)	0

Mod = Moderate

* Adverse events occurring after the first facial injection.

As detailed in Table 1, 123 of the 149 subjects who were treated with E
EVOLENCE® and 130 of the 149 subjects who were treated with the HA Control
product reported injection site reactions. Of those reported, in the **EVOLENCE®**
group 326 reactions were reported as mild, 18 as moderate and 3 severe. In the HA
Control group, 359 reactions were reported as mild, 31 as moderate and 1 severe.

The following disorders at the injection site were reported as either **EVOLENCE®** -
related or HA Control Product-related in at least 5% of the subjects: pain, erythema,
swelling, bruising, pruritus, and induration. Adverse events in this category that
occurred more commonly ($\geq 5\%$ difference) for HA Control Product Vs.

EVOLENCE® treated patients respectively, were site pain (63.8% vs. 56.4%),
swelling (68.5% vs. 53.7%) and bruising (47.7% vs. 36.2%) The only AE to occur
more commonly in the **EVOLENCE®** treated group ($\geq 5\%$ difference) was induration
(13.4% vs. 6.0%).

No other AEs were reported to be related to either **EVOLENCE®** or HA Control
Product in more than 2 subjects (1.3%). Serious AEs reported in 2 subjects were
Atrial septal defect and Metastatic colon cancer to ovaries.

Table 2: Number (%) of Subjects with Skin Reactions (Occurring in >5% of Subjects) to Study Product by Injection and Maximum Duration, as Reported in Subjects' Diaries and Physician Case Report Forms

	After First Facial Injection*							
	EVOLENCE® (N = 149)				HA Control Product (N = 149)			
Duration (Days)	≤ 3	4-7	8-14	>14	≤ 3	4-7	8-14	>14
No. of Subjects [†]	<u>96</u> (64.4)	<u>66</u> (44.3)	<u>17</u> (11.4)	<u>17</u> (11.4)	<u>99</u> (66.4)	<u>70</u> (47.0)	<u>28</u> (18.8)	<u>13</u> (8.7)
No. of Episodes	<u>200</u>	<u>94</u>	<u>25</u>	<u>21</u>	<u>209</u>	<u>124</u>	<u>34</u>	<u>21</u>
Erythema [‡]	<u>52</u> (34.9)	<u>21</u> (14.1)	<u>4</u> (2.7)	<u>3</u> (2.0)	<u>48</u> (32.2)	<u>27</u> (18.1)	<u>4</u> (2.7)	<u>4</u> (2.7)
Swelling [‡]	<u>43</u> (28.9)	<u>21</u> (14.1)	<u>8</u> (5.4)	<u>2</u> (1.3)	<u>54</u> (36.2)	<u>31</u> (20.8)	<u>5</u> (3.4)	<u>7</u> (4.7)
Induration [‡]	<u>6</u> (4.0)	<u>2</u> (1.3)	<u>1</u> (0.7)	<u>7</u> (4.7)	<u>2</u> (1.3)	<u>3</u> (2.0)	<u>1</u> (0.7)	<u>2</u> (1.3)
Bruising [‡]	<u>19</u> (12.8)	<u>22</u> (14.8)	<u>7</u> (4.7)	<u>1</u> (0.7)	<u>16</u> (10.7)	<u>31</u> (20.8)	<u>16</u> (10.7)	<u>4</u> (2.7)
Pain [‡]	<u>48</u> (32.2)	<u>24</u> (16.1)	<u>5</u> (3.4)	<u>5</u> (3.4)	<u>57</u> (38.3)	<u>27</u> (18.1)	<u>7</u> (4.7)	<u>3</u> (2.0)
Pruritus [‡]	<u>17</u> (11.4)	<u>2</u> (1.3)	<u>0</u>	<u>1</u> (0.7)	<u>17</u> (11.4)	<u>3</u> (2.0)	<u>1</u> (0.7)	<u>0</u>
	After Second Facial Injection [§]							
	EVOLENCE® (N = 74)				HA Control Product (N = 74)			
Duration (Days)	≤ 3	4-7	8-14	>14	≤ 3	4-7	8-14	>14
No. of Subjects [†]	<u>32</u> (43.2)	<u>12</u> (16.2)	<u>4</u> (5.4)	<u>6</u> (8.1)	<u>35</u> (47.3)	<u>20</u> (27.0)	<u>3</u> (4.1)	<u>4</u> (5.4)
No. of Episodes	<u>57</u>	<u>21</u>	<u>6</u>	<u>9</u>	<u>65</u>	<u>29</u>	<u>4</u>	<u>5</u>
Erythema [‡]	<u>14</u> (18.9)	<u>4</u> (5.4)	<u>3</u> (4.1)	<u>4</u> (5.4)	<u>12</u> (16.2)	<u>9</u> (12.2)	<u>1</u> (1.4)	<u>3</u> (4.1)
Swelling [‡]	<u>13</u> (17.6)	<u>8</u> (10.8)	<u>0</u>	<u>1</u> (1.4)	<u>17</u> (23.0)	<u>6</u> (8.1)	<u>2</u> (2.7)	<u>1</u> (1.4)
Bruising [‡]	<u>5</u> (6.8)	<u>3</u> (4.1)	<u>0</u>	<u>1</u> (1.4)	<u>5</u> (6.8)	<u>7</u> (9.5)	<u>0</u>	<u>1</u> (1.4)
Pain [‡]	<u>14</u> (18.9)	<u>5</u> (6.8)	<u>2</u> (2.7)	<u>2</u> (2.7)	<u>22</u> (29.7)	<u>5</u> (6.8)	<u>1</u> (1.4)	<u>0</u>
Pruritus [‡]	<u>4</u> (5.4)	<u>0</u>	<u>1</u> (1.4)	<u>0</u>	<u>4</u> (5.4)	<u>2</u> (2.7)	<u>0</u>	<u>0</u>
Induration [‡]	<u>3</u> (4.1)	<u>0</u>	<u>0</u>	<u>1</u> (1.4)	<u>1</u> (1.4)	<u>0</u>	<u>0</u>	<u>0</u>

* Reactions started between the day of first injection and 13 days after the day of first injection, or before touch-up injection.

† Number of subjects with at least 1 episode of specified duration.

‡ Duration = Maximum number of consecutive days with symptom from onset until resolution.

§ Reactions occurring from the day of injection through Day 13 after the second injection.

Note: The incidence of induration after the second injection was <5% for both devices.

The majority of the skin reactions at either the **EVOLENCE®** or the HA Control Product injection sites were of <4 days duration and almost all of them were less than one week in duration.

Non Local Adverse events considered to be non-device related, occurred in 41/149 (27.5%) of the study subjects. Since each subject received both EVOLENCE and HA based control treatment, the causality of these events could not be identified. These events included Infections and Infestation (10.1%) (upper respiratory infection, nasopharyngitis, sinusitis); Skin and Subcutaneous tissue disorder (5.4%) (actinic keratosis); Hypercholesterolemia (2%); Psychiatric disorder (2%)(anxiety).

Use of EVOLENCE® in Skin of Color Patients

Of the 149 subjects randomized in the US pivotal study, twenty two (22) had skin tones of light brown (Fitzpatrick skin tone IV), six (6) had skin tones of brown (Fitzpatrick skin tone V), and no subjects had skin tone of black (Fitzpatrick skin tone VI). In a separate skin challenge study, two (2) subjects had skin tone of brown (Fitzpatrick skin tone V). Twenty nine (29) subjects in France, Canada and Germany (i.e., twenty eight (28) with FP skin tone V and one with FP skin tone VI had EVOLENCE® injected in a post marketing setting. None of these subjects experienced hyperpigmentation or keloid formation.

Skin Challenge Study - Hypersensitivity

In an open-label, non-controlled, single-center study, 530 subjects were injected with two sequential intradermal **EVOLENCE®** skin test injections (two week interval), to evaluate the risk of developing localized hypersensitivity. Of the 519 subjects that completed the study period, there were no clinical observations of hypersensitivity, as measured by clinical and patient observation of local responses and laboratory measurement of immunological (antibody) responses. (Positive hypersensitivity reaction was defined as erythema persisting more than 72 hours plus positive histopathology biopsy assessment of the site biopsy). .

In addition no serious adverse events or unexpected adverse events occurred during the study period. Overall, 62 subjects reported 95 adverse events over the course of the study. 17 of the 95 adverse events were considered related to the treatment. No adverse events resulted in discontinuation from the study participation. All reported adverse events with two or more occurrences in this hypersensitivity study are listed in Table 3.

Table 3: All Adverse Events Reported on or after One Skin Test Injection in >1 Subject (n=530)

Description of AE	Number	Frequency (%)
Headache	8	1.5
Injection Site Erythema	5	0.9
Injection Site Discomfort	6	1.1
Injection Site Pruritus	6	1.1
Nasopharyngitis	5	0.9
Pharyngeal Pain	3	0.6

Nasal congestion	3	0.6
Dizziness	3	0.6
Influenza	3	0.6
Myalgia	2	0.4
Sinusitis	2	0.4
Cystitis	2	0.4
Cough	2	0.4
Pryexia	2	0.4
Joint injury/sprain	2	0.4
Vomiting	2	0.4
Contact dermatitis	2	0.4
Contusion	2	0.4

Related adverse events occurring in a single patient included swelling, injection site discoloration and injection site irritation. Other events occurring in a single patient, included injection site anaesthesia, fatigue, tenderness, aches, pains, sprains, injuries, anxiety, heart rate increase, herpes zoster, hyperhydrosis, ear infection, bronchitis, tooth infection, nausea, migraine, rash, increased tear production, ocular redness, and outpatient non-related surgical procedures.

One subject experienced erythema, tenderness and induration at the second skin test site (right forearm) more than two months post the End of the Study (more than three months after dosing of the second skin test). Histopathology from the biopsy site indicated that a positive hypersensitivity reaction was occurring. No sequelae were noted at the first skin test site (left forearm). Sera from this subject displayed positive titers for porcine collagen at study baseline prior to **EVOLENCE**[®]-Test injection and titers of sera from this subject remained positive up to the end of the study.

Other adverse event information - In postmarket studies for **EVOLENCE**[®] use outside the US, the type, severity, and duration of adverse events has not varied from the adverse events reported in Table 3, above.

CLINICAL STUDIES

a) Pivotal Study

Study Design:

“A randomized, comparative, multi-center, within subject (split-face) clinical trial was conducted to compare the safety and efficacy of **EVOLENCE**[®] Collagen Filler versus Control ([HA Control Product]) for the correction of soft tissue contour deficiencies.”

Subjects were screened and tested for hypersensitivity to porcine collagen by injecting 0.1 mL of **EVOLENCE**[®]-Test. Subjects with a positive reaction within approximately 4 weeks of the injection were to be discontinued from the study. Blood samples were collected prior the treatment and during follow up visits for determination of collagen antibody titers.

Eligible subjects meeting all inclusion/exclusion criteria were randomized and received injections of investigational device and comparator into their nasolabial folds.

Each subject was injected with **EVOLENCE®** into one nasolabial fold (NLF) and Hyaluronic Acid-based dermal filler (HA Control Product) into the contralateral NLF.

Treatment was considered to be complete when Optimal Cosmetic Result (OCR) was achieved, as determined by the judgment of the Principal Investigator. Subjects could receive one touch-up injection with either **EVOLENCE®** or the Control 2 weeks later in order to achieve OCR.

The OCR evaluation for both sides was approximately 2 weeks after the initial injection if no touch-up had been given, or 1 week after the touch-up injection. The OCRs evaluation was performed on both sides at the same time. Routine follow up visits for safety and effectiveness occurred at 3 month intervals post OCR visit through 12 months after the last treatment.

Adequacy of masking of the subject and the Blinded Evaluating Investigator (BEI) was checked following each facial injection, and at 6 and 12 months post OCR visit. Standardized facial photography was taken prior to treatment and during the study follow up. The BEI evaluated the severity of the subjects NLF's using a validated 7-point photographic grading scale Modified Fitzpatrick Wrinkle Scale (MFWS). BEI and subject self satisfaction with the overall treatment response using the Global Improvement Assessment scale (GIA), ranging from 1=much better to 4=worse, after each injection session and at each follow-up visit was conducted.

Study End points:

The primary efficacy endpoint for the study of **EVOLENCE®** for the correction of the nasolabial folds was compared to the control, as determined by BEI's live evaluation of the NLF severity score (utilizing MFWS) at the 6-month post- OCR visit. The statistical objective was to demonstrate non-inferiority of the **EVOLENCE®** to the control.

Safety was evaluated by comparing the incidence and severity of local and systemic adverse events reported by the treating investigator from the pretreatment skin testing through the 6-month post-OCR visit.

Additional analysis included BEI and subject satisfaction (utilizing GIA) with the overall treatment response; measurements of anti-porcine collagen antibodies and comparison of total volume of **EVOLENCE®** injected to the NLF to achieve OCR Vs. the study control.

Study Population:

A total of 149 (30-74 years of age) subjects were treated and 148 (90.2%) completed the 6 month follow-up period. Demographics are outlined in table 5 below.

Table 4: Subject Demographics –ITT Population

	Number (%) of Subjects
	ITT (N = 149)
Gender – n (%)	
Male	12 (8.1)
Female	137 (91.9)
Age (yr)	
Mean ± SD	55.7 ± 8.3
Range	30.4 – 73.8
Race – n (%)	
White	138 (92.6)
Asian	1 (0.7)
Native Hawaiian or other Pacific Islander	0
Black or African American	4 (2.7)
American Indian or Alaska Native	0
Other	6 (4.0)
Ethnicity – n (%)	
Hispanic/Latino	18 (12.1)
Not Hispanic/Latino	131 (87.9)
Skin Tone – n (%)	
I to III Pale White/White	121 (81.2)
IV Light brown	22 (14.8)
V Brown	6 (4.0)
VI Black	0
Mean pretreatment MFWS Severity Score	
EVOLENCE®	2.38
Restylane®	2.37

Efficacy Results:

EVOLENCE® was found to be non inferior to the control in the correction of NLF. During the 6 month follow up there was no statistically significant difference between **EVOLENCE®** and the HA Control Product with regard to the measure of improvement at any time point (See Table 5).

Table 5: Change in Modified Fitzpatrick Wrinkle Scale (MFWS) – Blinded Evaluating Investigator's Assessment – ITT Population (n=149)

	EVOLENCE®	HA Control Product	Difference
Screening			
N	149	149	149
Mean ± SD	2.38 ± 0.36	2.37 ± 0.36	0.01 ± 0.30
OCR Visit			
Mean ± SD	0.53 ± 0.52	0.50 ± 0.48	0.03 ± 0.35
Change from Screening at OCR			
Mean ± SD	-1.85 ± 0.50	-1.87 ± 0.45	0.02 ± 0.41

Observed Value at 3 months			
Mean ± SD	0.76 ± 0.65	0.71 ± 0.62	0.05 ± 0.48
Change from Screening at 3 months			
Mean ± SD	-1.62 ± 0.56	-1.66 ± 0.55	0.04 ± 0.48
Observed Value at 6 months			
Mean ± SD	0.92 ± 0.65	0.87 ± 0.69	0.05 ± 0.53
Change from Screening at 6 months			
Mean ± SD	-1.46 ± 0.57	-1.50 ± 0.60	0.04 ± 0.52

SD= standard deviation; Ranged from 0=No wrinkle – 3=Deep wrinkle

Antibody Testing:

The ELISA results indicate that multiple injections of **EVOLENCE®** for test and treatment did not result in development of antibodies against porcine type I collagen during this study of any clinical significance. With respect to IgG titers, 117 (80%) of the subjects were negative at all time points. 13 (8.8%) of the subjects displayed positive titers at both the Enrollment and Follow Up Visits of the study. 10 (6.8%) of the subjects changed status from negative to positive titers during the study. 3 subjects (2%) were borderline at enrollment and remained borderline at the end of the study and 1 subject (0.7%) changed from borderline to positive..

Notably the 14 subjects with elevated titers of antibodies to porcine collagen did not display any unusual adverse events with respect to incidence or characteristics, or any evidence of clinical symptoms compared to the general patient population. Of the 14 subjects with elevated titers post treatment, 10 subjects experienced adverse events at the injection site. These injection site adverse events were reported for both the EVOLENCE injection site and the HA Control product injection site. This proportion of adverse events (10/14, 71%) is similar to that observed in the entire Evolence population (126/149, 84.6%). All reactions observed in the 10 subjects with elevated titers were mild in severity and transient.

b) Skin Challenge Study of Hypersensitivity

Study Design

Prospective open label, non-controlled, single center clinical study with two sequential skin test injections were used to evaluate the risk of developing localized immune hypersensitivity.

In the initial visit baseline blood sample for anti- porcine collagen type I antibodies was obtained. The second visit consisted of the first skin test (0.1mL of EVOLENCE® -Test injected intradermally in the mid-volar, left forearm) to produce a bleb. Subjects then returned in approximately 72 hours for an evaluation of the skin test. All subjects who proved non-reactive to the first skin test were injected with a second skin test in the contra-lateral volar forearm after approximately 14 days. Approximately 72 hours after second injection, subjects returned for evaluation of the skin test sites and they returned again after ~30 days for evaluation. A second and final blood sample for anti- porcine collagen type I antibodies was taken at the final visit. The tested sites were monitored daily by the subject for signs of systemic and local reactions.

Healthy volunteers (18 years of age or older) were enrolled. Main exclusion criteria were: pregnant and/or nursing subjects; subjects treated with chemotherapy agent or systemic corticosteroids within the past 3 months; subjects with known allergy to collagen; subjects with a history of autoimmune disorder; subjects with severe allergies manifested by a history of anaphylaxis; or subjects with a current disease state that can affect immune response.

Study Objectives

The purpose of this study was to demonstrate that the risk of experiencing hypersensitivity to a double skin test with porcine collagen implants was less than 1.3%. A risk of 1.3% - 1.5% is the estimated risk of developing hypersensitivity complications during facial treatments with injectable bovine collagen for subjects who were initially negative to the bovine collagen skin test.

Study Population

Fife hundred and thirty (530) subjects were enrolled into the study consisting of 104 males and 426 females. The subjects' ages ranged from 18 to 92. 519 subjects completed the study and were included in the evaluable population. 530 subjects were included in the safety population evaluation. In this study two (2) subjects had skin tone of brown (Fitzpatrick skin tone V).

Results

Of the subjects who received 2 sequential skin tests, no subject displayed a positive hypersensitivity response against **EVOLENCE®**-Test (erythema grade moderate or severe reaction). All subjects who displayed mild and mild to moderate erythema and did not exceed the initial bleb size of the implanted **EVOLENCE®**-Test. No induration was observed.

Post Study Observation:

One subject displayed delayed local positive hypersensitivity reaction of increasing redness, swelling and tenderness at the right volar forearm (2nd injection site) more than two months post the end of the study (more than 3 months after injection of the second **EVOLENCE®** skin test).

Conclusions:

No instance of hypersensitivity was observed during the study period. The upper bound of the one-sided exact 95% confidence interval for subjects experiencing strong to severe reactions to the **EVOLENCE®** skin test is 0.58%. Based on these findings no pre-treatment skin testing is required.

DIRECTIONS FOR USE

EVOLENCE® Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

Assembly of Needle to Syringe:

For safe use of **EVOLENCE®** it is important that the needle is properly assembled onto the syringe. Use the 27GX1/2" needle provided.

1. Carefully unscrew the syringe tip cap while securely holding the syringe Luer adapter.
2. With a loose grip on the narrow part of the needle shield, mount the needle on the Luer-syringe lock by screwing clockwise until counter pressure is felt.
3. With a firm grip on the wider part of the needle shield, press and turn the needle further until secure (approximately a quarter turn).
4. Remove the needle shield by pulling the shield straight away from the syringe, ensuring not to twist the shield during removal.

Injection of EVOLENCE® Collagen Filler:

1. Prior to treatment with **EVOLENCE®** the patient should be fully apprised of the indications, contraindications, warnings, precautions, adverse events and method of administration. A complete medical history should be obtained to ensure suitability for treatment. Patient also should be advised that a supplemental "touch-up" injection may be required to achieve and maintain optimal correction.
2. The patient's wrinkle or fold should be characterized with regard to etiology, distention, stress at site and depth of lesion. Pretreatment photographs are recommended.
3. Topical and/or injectable anesthesia may be used to manage pain during and after injection.
4. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or another antiseptic substance.
5. Before injecting the patient, depress the plunger until the product flows out of the needle.
6. The needle should be placed in a sterile manner into the plane(s) of apparent deformity.
7. The injection technique of **EVOLENCE®** with regard to the angle and orientation of the bevel, the depth of injection and the quantity administered may vary. A linear threading technique, tunneling technique, serial puncture injections or combinations have been used to achieve optimal results.
8. For linear threading technique and/or tunneling technique the needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. The bevel of the needle should face upward and the substance should be injected into the mid to deep dermis. This can be ascertained by observing a subtle elevation of the defect without any blanching following injection.
9. If **EVOLENCE®** is injected too superficially this may result in visible lumps and or discoloration.
10. Inject **EVOLENCE®** by applying even pressure on the plunger rod while slowly pulling the needle backwards. The wrinkle should be lifted and eliminated by the end of the injection. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
11. Correct to 100% of the desired contour effect. Do not overcorrect. With cutaneous contour deformities the best results are obtained if the defects can be manually stretched to the point where it is eliminated.

The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the injected site, the depth of the implant in the tissue and the injection technique.

12. If immediate blanching occurs, this could be an indication that the device injection is too superficial. The injection should be stopped and the area massaged until it returns to a normal color. When the injector continues treatment, they should assure that the appropriate injection depth is reached.
13. When injection is complete, the treated side should be gently massaged so it conforms to the contour of the surrounding tissues. In the event of unintentional overcorrection, massage the area firmly between your fingers or against an underlying superficial bone to obtain optimal results.
14. Needles may become occluded or dull during a treatment session, and needle replacement may be necessary.
15. With patients who have localized swelling, the degree of correction is sometime difficult to judge at the time of treatment. In this case it is better to invite the patient to a touch-up session after 1-2 weeks. Although the company has not observed severe reactions during treatment in the 668 subjects injected in the US **EVOLENCE**[®] clinical trials, in the event that severe swelling or a systemic reaction occurs during injection, discontinue treatment and contact OrthoNeutrogena (1-800- 386-5362).
16. Corrective touch up injection may be required to achieve optimal correction of the contour. If the deformity needs further treatment the same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as deformity severity, skin elasticity and dermal thickness at the treatment site.
17. Patients may have mild to moderate injection site reactions, which typically resolved in a few days.
18. Severely indurated defects which initially resist distention may require several treatment sessions before desired correction is obtained. In such defects, it is preferable to fill within the indurated defect rather than beneath it.
19. The physician should instruct the patient to report any problems possibly associated with the use of **EVOLENCE**[®].

PATIENT INSTRUCTIONS

It is recommended that the following information be shared with patients:

- Within the first 24-48 hours patients should avoid :
 - Strenuous exercise
 - Excessive sun, extreme heat, or extreme cold exposure
 - Alcoholic beverages

Exposure to any of the above may cause temporary redness, swelling and/or itching at the injection sites.

- To report an adverse reaction, call OrthoNeutrogena (1-800- 386-5362).

HOW SUPPLIED

EVOLENCE® Collagen Filler is supplied in single use glass syringe with a luer- lock fitting. The product is presented as a sterile, non-pyrogenic gel in 1.0 mL syringe. Fill volume varies between presentation and is stated on the syringe label and carton.

Sterilized needles 2X 27GX 1/2" are packed beneath the transparent blister insert. In order to use the needles, gently pull up the insert and expose the needle pack beneath it. Three patient record labels are provided. Do not use if package is opened or damaged.

STERILE NEEDLES

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.

STORAGE

- **EVOLENCE®** should be stored at room temperature, between 59°F-86°F (15°C-30°C). Avoid refrigeration and freezing. Protect from sunlight.
- **EVOLENCE®** is a yellowish, homogenous, opaque gel. In the event that a syringe contains material exhibiting separation between solid and liquid, or change of color, do not use the syringe and notify OrthoNeutrogena immediately at 1-800- 386-5362.

STERILITY

EVOLENCE® Collagen Filler collagen filler is for single use only. The content of the syringe is manufactured by validated aseptic production processes and should be used immediately after opening. Discard any unused **EVOLENCE®**. The needles supplied with the package are sterile.

Sterility is maintained only if the syringe and packaging of the needles are intact and undamaged.

Symbols



Attention, see instructions for use



Do not reuse



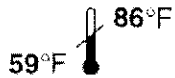
Use by/Expiration Date



Lot/Batch number



Processed using aseptic process;
Only the content of the syringe is sterile



Temperature limitation

REF

Catalogue number

MANUFACTURED BY:

ColBar LifeScience Ltd.

P.O. Box 12206

Herzliya 46733

ISRAEL

Tel: +972-9-971-8666

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DISTRIBUTED BY:

OrthoNeutrogena division of Ortho-McNeil-Janssen-Pharmaceuticals, Inc.

Los Angeles, CA 90045

EVOLENCE® is a registered trademark of ColBar LifeScience Ltd.

US Patent Number: 6,682,760.

EVOLENCE® Collagen Filler Instructions for Use, 100044 Ver. 05, June 2008

EVOLENCE® Collagen Filler

(Injectable GLYMATRIX™ Collagen Dermal Filler)

PATIENT INFORMATION

Review this brochure carefully before beginning your EVOLENCE® Collagen Filler Treatment

The information in this brochure is not meant to replace information provided by your healthcare provider. You should always ask your healthcare provider about your treatment and care

GLOSSARY

Anesthetic: A product that can cause a temporary loss of feeling or awareness. Anesthetics can be applied topically or injected for a local effect.

Collagen: The most common protein found in the body. Collagen is used to form a framework to support cell and tissue growth.

Crosslinking: Linking two different elements to create a new matrix/structure.

Dermal Filler: A product that is injected underneath the skin. Fillers are used to decrease the appearance of fine lines or wrinkles.

GLYMATRIX™: The unique patented technology used in **EVOLENCE®** to crosslink the collagen with sugar (ribose) to provide strength and long-lasting characteristics.

Hyaluronic Acid (HA) based filler – Filler made using a natural, complex sugar found within the body

Induration: A hard or thick area of the skin or tissue.

Injection: When a product is given with a needle.

Natural: Found in nature.

Porcine: Of pig origin. Medical products of porcine origin include heart valves, wound dressings, and lens implants.

Ribose: Ribose is a natural sugar and building block used by the body.

Side Effect: An unwanted event caused by the use of a product.

Synthetic: Man made.

WHAT IS EVOLENCE® COLLAGEN FILLER?

EVOLENCE® collagen dermal filler products are used to correct facial wrinkles and folds. **EVOLENCE®** is made of highly purified porcine collagen that is crosslinked via GLYMATRIX™ technology to provide long lasting results.

WHAT IS EVOLENCE® COLLAGEN FILLER USED FOR?

EVOLENCE® is injected into areas of facial tissue where moderate to deep facial wrinkles and folds occur.

WHO CAN BENEFIT FROM EVOLENCE® COLLAGEN FILLER TREATMENT?

EVOLENCE® may be appropriate for patients who want soft, supportive foundation to fill areas where there has been natural collagen loss. Your healthcare provider can help you determine if you are a good candidate for **EVOLENCE®** treatment.

DO I NEED A SKIN TEST BEFORE USING EVOLENCE® COLLAGEN FILLER?

No. Skin test studies showed that reactions to **EVOLENCE®** are rare and, when they do occur, mild. Skin testing is not necessary prior to treatment. However, in case you have had an allergy to collagen product in the past (such as hives or swelling after eating porcine products) or serious recurrent nonspecific allergic reactions, please inform your healthcare provider before treatment.

WHAT SHOULD MY HEALTHCARE PROVIDER WARN ME ABOUT?

- **EVOLENCE®** should be used with caution in patients on immunosuppressive therapy (medication commonly prescribed for those who have undergone an organ transplant, or are suffering from rheumatoid arthritis, psoriasis, inflammatory bowel disease, or cancer).
- The safety and effectiveness of **EVOLENCE®** for the treatment of areas other than facial wrinkles and folds have not been established in controlled clinical studies.
- **EVOLENCE®** should be used with caution in patients with known connective tissue disease, such as rheumatoid arthritis, scleroderma or systemic lupus erythematosus, history of herpes.
- The safety of **EVOLENCE®** in pregnant or breastfeeding women as well as in patients under the age of 18 years has not been established.

CAN EVOLENCE® BE USED IN SKIN OF COLOR PATIENTS?

The safety of **EVOLENCE®** Collagen Filler in skin of color patients (*i.e.*, individuals with skin tone of light brown to black) was studied for a limited time only (2 weeks to 3 months, 3 to 6 months, and greater than 6 months). **EVOLENCE®** should not be used in patients with known susceptibility to abnormal scarring or local changes in skin color. The safety of **EVOLENCE®** in patients susceptible to keloid formation, hyperpigmentation and hypertrophic scarring has not been established.

WHO SHOULD NOT USE EVOLENCE® COLLAGEN FILLER?

- Patients with a known allergy from eating any pork collagen product
- Patients with a history of severe or multiple occurring allergies.

People with these conditions, if they use **EVOLENCE®**, may have an allergic reaction and experience swelling, redness, or pain. In rare instances, allergic reactions to some materials can be severe and require medical assistance. Although no such reaction has ever been observed following use of **EVOLENCE®**, patients having experienced past allergic reactions to pork products should be aware of their medical history and these risks.

HOW DOES EVOLENCE® COLLAGEN FILLER WORK?

The production of collagen in the body decreases as you get older and/or exposed to the sun. The first visible signs of this decrease in production are the development of wrinkles. **EVOLENCE®** works by replacing and restoring collagen in the dermal layer of the skin where it naturally exists. **EVOLENCE®** will be injected with a fine needle midway or deep into your skin to help fill the areas of lost collagen where moderate to deep facial wrinkles and folds occur.

HOW IS EVOLENCE® COLLAGEN FILLER INJECTED?

EVOLENCE® is injected beneath the wrinkle or fold into the dermal layer of the skin using a fine needle.

DO INJECTIONS HURT?

Dermal fillers often require more than one injection during a treatment session to obtain an optimal result. The use of a needle to inject a product like a dermal filler can be associated with local skin discomfort. Certain areas of the face are more sensitive than others and your healthcare provider may choose either an external and/or local injectable anesthetic to help prevent discomfort and pain. Discuss pain management with your healthcare provider.

ARE THE RESULTS FROM EVOLENCE® COLLAGEN FILLER IMMEDIATE?

Yes. The natural collagen structure of **EVOLENCE®** fills the space of the depleted collagen and decreases the appearance of wrinkles, so it immediately gives the skin a smoother appearance.

HOW MANY TREATMENTS ARE REQUIRED?

One treatment with **EVOLENCE®** may be all that is required to achieve optimal wrinkle smoothing. The decision for additional treatments with **EVOLENCE®** is left up to you and your healthcare provider. Your healthcare provider will generally like to see you within two weeks of the first treatment to assess your satisfaction and to measure the success of treatment.

Following your initial treatment, you and your healthcare provider will determine when future injections are needed.

HOW LONG DOES EVOLENCE® COLLAGEN FILLER LAST?

The length of time that **EVOLENCE®** lasts in the body may vary from patient to patient. The duration may also depend on the amount of **EVOLENCE®** injected and the injected area. Information from a US clinical trial has shown that 97% of

the patients maintained the effects of **EVOLENCE®** for at least 6 months. Data gained from animal studies, foreign clinical studies and usage of **EVOLENCE®** in other countries have demonstrated that **EVOLENCE®** has lasted for up to 12 months.

WHAT CAN I EXPECT TO HAPPEN AT A TREATMENT SESSION?

- Your healthcare provider will answer any questions you have before your treatment.
- Remove all make-up prior to your treatment.
- An antiseptic will be used to clean all of the areas to be treated.
- Local anesthetics will be used if needed.
- Small amounts of **EVOLENCE®** will be injected into the skin.
- You will then receive instructions on how to care for the treated area once you leave the office.

WHAT CAN I EXPECT AFTER TREATMENT?

Immediately after your treatment, the injection sites may be painful and red or swollen. These site reactions are typically mild and go away with time, usually within hours to a few days. Follow the post-treatment directions given to you by your healthcare provider. If a side effect lasts longer than expected and is of concern to you, contact your healthcare provider. You might have a mild to moderate reaction at the injection site, but that should clear up in a few days.

You should follow these instructions.

- Within the first 24-48 hours you should avoid.
 - Strenuous exercise
 - Excessive sun, extreme heat, or extreme cold exposure
 - Alcoholic beverages

Exposure to any of the above may cause temporary redness, swelling, or itching at the injection site.

WHAT DID CLINICAL STUDIES SHOW?

EVOLENCE® collagen filler was studied in 149 patients who were injected with **EVOLENCE®** on one side of the mouth and a Hyaluronic Acid based filler on the other. The most common injection-related side effects include pain, redness, and swelling. The majority of these side effects (80%) were mild and disappeared within 1-7 days of injection. The percentage of the common injections site reactions are represented in the table below:

Injection Site Reactions (occurred in >5% of patients; # of patients =149)				
	EVOLENCE®		Restylane®	
	# of patients	% of patients	# of patients	% of patients
Total # of subjects	123	82.6	130	87.2
Injection site pain	84	56.4	95	63.8
Injection site redness (erythema)	86	57.8	89	59.7
Injection site swelling	80	53.7	102	68.5
Injection site bruising	54	36.2	71	47.7
Injection site itching (pruritus)	23	15.4	25	16.8
Injection site hardness (induration)	20	13.4	9	6.0

Other rare side effects of dermal fillers include the development of small lumps in the skin at the treated areas. While these lumps may not be visible and may go away with time, you or your doctor may notice them when the treated area is pressed upon.

As with any skin injection, there is a risk of infection.

Please report any side effect to your healthcare provider.

WHAT SHOULD I TELL MY HEALTHCARE PROVIDER ABOUT THE MEDICATIONS I TAKE?

Talk with your doctor about all medications that you are taking. In addition, discuss over-the-counter medications and natural products that you are using on a regular basis. It is also recommended that you tell your doctor about other fillers or procedures you have had in the past. If you are taking a blood thinner or medications that may interfere with clotting of the blood such as aspirin, Ibuprofen or Vitamin E products, you may be more likely to develop bruising at the sites of injection.

No formal drug interaction studies have been done with **EVOLENCE®**. Talk with your healthcare provider about your medical history prior to deciding on a specific treatment.

WHEN SHOULD I NOTIFY MY HEALTHCARE PROVIDER IF I HAVE CONCERNS?

Any side effect that lasts longer than a week should be reported to your healthcare provider. Call your healthcare provider if you are concerned about your side effect or think that you have a complication.

HOW QUICKLY CAN I GET BACK TO MY DAILY ACTIVITIES?

The majority of patients who receive **EVOLENCE®** collagen filler injections continue with their daily activities following treatment. However, during the first 24-48 hours after treatment, exposure to extremes of temperature (hot or cold) or strong sunlight should be avoided to reduce risk of inflammation. After this time you can go about your normal daily activities with no other treatment required.

**WHEN WILL I BE ABLE TO APPLY MAKE-UP AFTER EVOLENCE®
COLLAGEN FILLER INJECTIONS?**

Do not apply make-up immediately after treatment to avoid any complications and to keep the treated area clean. You should ask your healthcare provider when make-up may be applied after treatment.

WHAT OTHER TREATMENTS ARE AVAILABLE TO ME?

There are a variety of treatments and/or dermal fillers available in the United States. Safety and effectiveness vary. You should consult with your healthcare provider to determine which one is right for you.

For further questions and information, or to report an adverse reaction, please call 1-800-386-5362

Prescribing information as of June 2008.

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